Parental History of Hypertension and Parental History of Diabetes and Microvascular Complications in Insulin-dependent Diabetes Mellitus: the EURODIAB IDDM Complications Study

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Diabetic nephropathy clusters in families, suggesting an inherited predisposition. Parental history of hypertension and of Type 2 diabetes mellitus have been associated with nephropathy in offspring with Type 1 diabetes in some studies but not in others. The associations of parental history of hypertension and of diabetes with both albuminuria and proliferative retinopathy were studied in a large cross-sectional study of 3250 patients with Type 1 diabetes, from 16 European countries. Albuminuria was associated with hypertension in a parent ($p < 0.01$ in men, $p < 0.05$ in women), adjusted for age. Patients with a parental history of hypertension had a higher prevalence of hypertension ($p < 0.001$ in men, $p < 0.01$ in women) and a higher prevalence of parental diabetes ($p < 0.001$ in men, $p < 0.001$ in women). The association of albuminuria with parental hypertension was independent of parental diabetes in men but not women (OR = 1.28 in men $p = 0.04$, OR = 1.25 in women $p = 0.09$) and was not independent of hypertension in the patient him/herself in either sex. Albuminuria was associated with parental diabetes in women only (OR = 1.36, $p = 0.04$). This association was independent of both parental hypertension and hypertension in the patient herself. Proliferative retinopathy was not associated with parental hypertension or diabetes. The implications of these data are that both candidate genes for hypertension and Type 2 diabetes should be considered in the search for the genetic determinants of diabetic nephropathy. © **1998 John Wiley & Sons, Ltd.**

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Introduction

The incidence of nephropathy in Type 1 diabetes mellitus increases with duration of diabetes, peaking at 15–20 years of diabetes duration and then declining.[1–3] This suggests an exhaustion of susceptible patients over time. The fact that some patients do not develop nephropathy despite poor glycaemic control also suggests that some other predisposing factor, possibly genetic, is required for the development of nephropathy.

Several studies have provided evidence for clustering of diabetic nephropathy in families.[4–6] Seaquist *et al*. found a relative risk of 5 for nephropathy in diabetic siblings of patients with diabetic nephropathy compared to diabetic siblings of normoalbuminuric Type 1 diabetes patients.[5] In a similar study, Borch-Johnsen *et al*. found an odds ratio of 4.9 of developing high microalbuminuria (101–300 mg $24\ h^{-1}$) if a diabetic sibling had nephropathy, compared to the odds in diabetic siblings of Type 1 diabetes patients without nephropathy.[4] In a prospective study, Quinn *et al*. found a higher incidence of persistent proteinuria in siblings of probands with advanced diabetic nephropathy than in siblings of diabetic probands without nephropathy (incidence rate ratio = 2.5).[6] Studies in the Pima Indians show that nephropathy also aggregates in families with Type 2 diabetes.[7,8]

Familial clustering of nephropathy may be due to a familial predisposition to hypertension which may be genetic. The genetic contribution to hypertension has been well recognized in the general population[9] and Type 1 diabetic patients who have a parental history of hypertension have higher blood pressures than those

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without.[10] Raised blood pressure is associated with albuminuria[11] and predates the development of albuminuria in most, but not all, prospective studies.[12,13] An association between parental hypertension or blood pressure and nephropathy in offspring has been reported.[14,15] However this association has not always been found.[16,17] Furthermore, although it has been suggested[15] that predisposition to hypertension has a role in nephropathy beyond simply increasing the blood pressure in offspring, this issue has not been specifically addressed.

Insulin resistance has been associated with microalbuminuria in Type 1 patients[18] and it has been suggested that such resistance or predisposition to Type 2 diabetes may play a role in the familial clustering of nephropathy. In support of this, a family history of cardiovascular disease[19] and Type 2 diabetes[20] have been associated with nephropathy in Type 1 diabetes patients, and recently cardiovascular risk factor levels have been found to be higher in parents of those Type 1 diabetes patients with raised albumin excretion rates (AER) compared with those with normal AER.[21]

The natural history of diabetic retinopathy is different from that of nephropathy. Although almost all Type 1 diabetes patients develop background retinopathy, not all will develop proliferative disease.[22–24] Like nephropathy, there is evidence for familial clustering of retinopathy[25] and for an association with HLA genotype.[26–29] However, two studies have failed to find any association between family history of high blood pressure and severe retinopathy. The association between family history of diabetes and retinopathy has been assessed in two studies but most of the patients had Type 2 diabetes.[30,31]

The EURODIAB IDDM Complications Study is the largest cross-sectional study of diabetic complications in persons with Type 1 diabetes. This article reports the association between parental history of diabetes and of hypertension with albuminuria and retinopathy in offspring who were members of this cohort. The extent to which any association between parental history of hypertension and albuminuria is independent of blood pressure in offspring was examined and the independence of the effect of parental history of hypertension from the effect of parental history of diabetes was assessed.

Patients and Methods

Subjects

The EURODIAB IDDM Diabetes Complications Study is a cross-sectional survey of 3250 people (51 % male) with Type 1 diabetes mellitus from 31 centres in 16 countries in Europe. Detailed methods have been published.[32] Briefly, a random sample of all clinic attendees aged 15–60 years in 1 calendar year, stratified by sex, age, and duration, were invited to take part; 85 % participated. Their mean age was 32.7 years (SD = 10.0) and mean diabetes duration was 14.7 years (SD = 9.3). Type 1 diabetes was defined as diabetes diagnosed before the age of 36 years with continued need for insulin within 1 year of diagnosis. Pregnant women, patients who were unrepresentative of local ethnic groups and those with diabetes for less than 1 year were not recruited. Data were collected between 1989 and 1990.

Methods

Urinary albumin was measured in a central laboratory by an immunoturbidimetric method[33] on a single 24-h collection, after the exclusion of infection, and the albumin excretion rate (AER) calculated. For the purpose of this analysis, patients with an AER $\geq 20\ \mu g\ min^{-1}$ were considered to have albuminuria, but the analyses were repeated with albuminuria defined at the higher AER of $\geq 100\ \mu g\ min^{-1}$ and with AER treated as a continuous variable. HbA_{1c} was measured by an enzyme immunoassay[34] with a laboratory reference range 2.9–4.8 %. Retinopathy was measured by photography of two retinal fields per eye. A single observer graded all retinal photographs by comparison with standard photographs. Proliferative retinopathy was defined as any new vessels, fibrous proliferations, vitreous haemorrhages or photocoagulation scars.[35] Current prescribed medications for high hypertension were recorded by the local investigator from clinical records. Sitting blood pressure was measured with a Hawksley Random Zero sphygmomanometer. Using an appropriately sized cuff, two blood pressure readings were taken from the right arm with the patient in a seated position after 5 minutes rest. Readings were taken from the top of the meniscus and measurement was recorded to the nearest 2 mmHg. Diastolic blood pressure was recorded at the disappearance of sound (fifth phase). Data presented here are based on the mean of the two measurements. Hypertension was defined either as taking antihypertensive agents or as a systolic blood pressure ≥ 160 mmHg or a diastolic pressure ≥ 95 mmHg. Waist circumference was measured to the nearest half centimetre at the midpoint between the upper iliac crest and lower costal margin in the midaxillary line. Hip circumference was measured at the level of the greater trochanters and waist to hip ratio (WHR) was calculated as waist cm/hip cm. Height without shoes was measured to the nearest half centimetre and weight was measured to the nearest half kilogram (indoor clothing, no shoes).

Parental history of hypertension and diabetes was obtained from the patient by a standard questionnaire asking whether either parent had ever been treated for high blood pressure and whether one or both parents had suffered from diabetes. Patients were also asked about a history of their own antihypertensive treatment. Patients with a positive parental history of diabetes (i.e. at least one parent with diabetes) were asked about parental use of insulin. Those with deceased parents were asked for the cause of death.

Statistical Analysis

The distribution of patient characteristics and prevalence of albuminuria and proliferative retinopathy was assessed according to parental history. Least-squares regression models were used for continuous variables to assess differences between group means, adjusting for age. For categorical variable the direct method was used to calculate prevalences standardized to the age distribution of the total sample and the extended Mantel-Haenszel chi-squared test was used to assess any differences between standardized prevalence rates. The independence of the association between parental history and both albuminuria and retinopathy in offspring was assessed using multiple logistic regression adjusting for other variables, including hypertension in the diabetes patient him/herself. As diabetes and hypertension are associated, the independence of the effect of parental history of hypertension from the effect of parental history of diabetes was assessed using logistic regression. In addition, an interaction between the effects of parental history of diabetes and hypertension was also sought by including an interaction term in the logistic regression model. Analyses were performed separately for men and women. The distribution of WHR was normalized by log transformation and the transformed variable used throughout the analysis, which was performed using the SAS statistical package.

The prevalence of albuminuria according to whether a parent had died from cardiovascular disease (myocardial infarction or stroke) was also examined.

Results

Albuminuria

In total 3250 patients participated (1668 men and 1582 women). Parental history of hypertension was not known for 13 % of men and 10 % of women and of diabetes for 3 % of men and 3 % of women. Thirty-one per cent of patients had albuminuria (AER $\geq$ 20 μg min^{-1}) and 11 % proliferative retinopathy. The prevalence of albuminuria and hypertension did not differ between those with and without data on family history. Two centres did not measure retinopathy, 771 photographs were ungradeable and 196 urine samples were unsuitable for measurement of albumin excretion.

Tables 1 and 2 show demographic and biochemical characteristics of the Type 1 diabetes patients by family history of hypertension and family history of diabetes. Five hundred and ninety-eight (41 %) men and 626 (44 %) women had at least one parent with a history of hypertension. Of those with a positive parental history, 12 % ($n = 144$) reported that both parents had hypertension. Men and women with a positive parental history of hypertension were older than those without hypertensive parents ($p < 0.001$). Among men, HbA_{1c} and WHR but not BMI or duration of diabetes were higher among those with than without a parental history of hypertension, adjusted for age (Table 1). Among women, BMI, but not duration, HbA_{1c} or WHR were higher among those with than without a parental history of hypertension, adjusted for age (Table 1). The prevalence of hypertension and a parental history of diabetes was higher among those with than without a parental history of hypertension, adjusted for age among both men and women (Table 1).

Two hundred and seventy-nine (17 %) men and 289 (19 %) women had at least one parent with diabetes. Of those with a positive parental history, both parents were affected in 5 % ($n = 30$). Maternal and paternal diabetes were equally common. Maternal diabetes constituted 51 % of all parental diabetes. Of parents with diabetes, 66 % had not used insulin. Both men and women with a positive parental history of diabetes were older than those without diabetic parents (Table 2). Among men, HbA_{1c} and WHR, but not BMI or duration of diabetes, were higher among those with than without a parental history of diabetes, adjusted for age (Table 2). Among women, there was no difference in BMI, duration, HbA_{1c} or WHR between those with and without a parental history of diabetes, adjusted for age (Table 2). The prevalence of a parental history of hypertension, but not hypertension in the patient him/herself, was higher among those with than without a parental history of diabetes, adjusted for age, among both men and women (Table 2).

Among men and women the prevalence of albuminuria was significantly higher in those with, compared to those without, a parental history of hypertension, adjusted for age (Table 3). The prevalence of albuminuria was also significantly higher in those with, compared to those without, a parental history of diabetes, adjusted for age in both sexes (Table 3).

Table 4 shows the results of the logistic regression analysis with the odds of albuminuria in those with compared to those without a positive parental history of hypertension. Men with a parental history were 1.34 times more likely to have albuminuria than those without ($p = 0.01$), adjusted for age. A similar odds ratio was observed in women (OR = 1.28, $p = 0.04$). Adjustment for HbA_{1c} made little difference to this result. In men, but not women, this association was independent of parental history of diabetes (OR = 1.28, $p = 0.04$ in men; OR = 1.25, $p = 0.09$ in women). On adjustment for hypertension in the patient him/herself however, the odds ratio was attenuated in both sexes and the association was no longer significant (OR = 1.15, $p = 0.3$ in men; OR = 1.18, $p = 0.2$ in women). This was true regardless of how adjustment for blood pressure status in the patient was made (Table 4). A parental history of hypertension did not modify the effect of hypertension in the patient him/herself on albuminuria ($p = 0.61$ and $p = 0.51$ for the interaction in men and women, respectively). When the association between AER and parental history of hypertension was examined with data from both sexes combined the conclusion was unchanged.

Table 1. Characteristics of patients by sex and family history of hypertension

	Men Family history of hypertension		Women Family history of hypertension	
	Positive $n = 598$ (41 %) Mean (95 % CI)[a]	Negative $n = 850$ (59 %) Mean (95 % CI)[a]	Positive $n = 626$ (44 %) Mean (95 % CI)[a]	Negative $n = 799$ (56 %) Mean (95 % CI)[a]
Age (yr)	34 (33,35)	31 (31,32)[e]	34 (33,35)	31 (31,32)[e]
Diabetes duration (yr)	13.7 (13.2,14.3)	14.4 (13.9,14.8)	14.9 (13.9,14.8)	15.1 (14.6,15.6)
HbA_{1c} (%)	6.8 (6.6,6.9)	6.5 (6.4,6.7)[c]	6.8 (6.6,6.9)	6.8 (6.6,6.9)
BMI (kg m^{-2})	23.7 (23.5,23.9)	23.4 (23.2,23.6)	23.7 (23.4,23.9)	23.3 (23.0,23.5)[c]
Waist to hip ratio[b]	0.89 (0.88,0.89)	0.88 (0.87,0.88)[c]	0.80 (0.79,0.80)	0.80 (0.79,0.81)
	% (95 % CI)[a]	% (95 % CI)[a]	% (95 % CI)[a]	% (95 % CI)[a]
Hypertension	20.9 (17.3,24.6)	13.5 (10.9,16.2)[e]	16.4 (13.3,19.6)	10.9 (8.5,13.3)[d]
Family history of diabetes	22.9 (19.0,26.7)	12.2 (9.8,14.6)[e]	23.2 (19.5,27.0)	13.5 (10.9,16.1)[e]

[a]Means and percentages are adjusted for age, with the exception of age where crude means are presented.
[b]Geometric means.
There is a significant difference between means/percentages for family history of hypertension +ve and –ve with [c]$p < 0.05$, [d]$p < 0.01$, [e]$p < 0.001$.
BMI, body mass index.

Table 2. Characteristics of patients by sex and family history of diabetes

	Men Family history of diabetes		Women Family history of diabetes	
	Positive $n = 279$ (17) Mean (95 % CI)[a]	Negative $n = 1343$ (83) Mean (95 % CI)[a]	Positive $n = 289$ (19) Mean (95 % CI)[a]	Negative $n = 1251$ (81) Mean (95 % CI)[a]
Age (yr)	36 (35,37)	32 (31,32)[e]	36 (35,37)	32 (31,32)[e]
Diabetes duration (yr)	13.8 (13.0,14.6)	14.5 (14.1,14.9)	14.6 (13.8,15.4)	15.0 (14.6,15.4)
HbA_{1c} (%)	7.0 (6.8,7.2)	6.6 (6.5,6.7)[d]	6.8 (6.6,7.0)	6.8 (6.7,6.9)
BMI (kg m^{-2})	23.8 (23.5,24.1)	23.5 (23.4,23.6)	23.5 (23.2,23.9)	23.5 (23.3,23.6)
WHR	0.89 (0.88,0.90)	0.88 (0.87,0.88)[c]	0.80 (0.79,0.81)	0.80 (0.79,0.80)
	% (95 % CI)[a]	% (95 % CI)[a]	% (95 % CI)[a]	% (95 % CI)[a]
Hypertension	16.9 (12.3,21.4)	15.8 (13.6,18.0)	14.6 (10.4,18.9)	12.4 (10.4,14.4)
Family history of hypertension	56.1 (46.4,65.8)	38.4 (34.5,41.5)[e]	57.7 (48.0,67.4)	40.9 (3725,44.6)[e]

[a]Means and percentages are adjusted for age, with the exception of age where crude means are presented.
[b]Geometric means.
There is a significant difference between means/percentages for family history of diabetes +ve and –ve with: [c]$p < 0.05$, [d]$p < 0.01$, [e]$p < 0.001$.
BMI, body mass index.

Albuminuria was associated with parental history of diabetes after adjustment for age and HbA_{1c} in women only (OR = 1.21 for men, $p = 0.18$. OR = 1.36 for women, $p = 0.04$, Table 5) This association among women persisted on further adjustment for parental history of hypertension and hypertension in the woman herself, regardless of how adjustment for blood pressure status in the woman was made (Table 5). Furthermore, among women parental history of diabetes accounted for the association between parental history of hypertension and albuminuria (Table 5). A parental history of hypertension did not modify the effect of a parental history of diabetes on albuminuria ($p = 0.58$, $p = 0.48$ for this interaction in men and women respectively, Table 5). The association between AER and parental history of diabetes, with data from both sexes combined, was not significant (OR = 1.3, CI 0.99–1.57, $p = 0.058$).

When the association between AER and parental history was examined with AER treated as a continuous variable the conclusions were unchanged. There was no independent association of parental history of hypertension with AER in men or women and in women parental history of diabetes continued to be independently associated with AER. With albuminuria defined as

Table 3. Association of albuminuria and proliferative retinopathy with family history of (a) hypertension and (b) diabetes

(a)

	Men Family history of hypertension		Women Family history of hypertension	
	Positive % (95 % CI)[a]	Negative % (95 % CI)[a]	Positive % (95 % CI)[a]	Negative % (95 % CI)[a]
Albuminuria	37.4 (32.3,42.5)	30.2 (26.3,34.0)[c]	31.2 (26.6,35.7)	25.8 (22.1,29.4)[b]
Proliferative retinopathy	11.8 (8.7,15.0)	8.9 (6.4,11.4)	12.7 (9.5,15.9)	12.5 (9.5,15.5)

(b)

	Men Family history of diabetes		Women Family history of diabetes	
	Positive % (95 % CI)[a]	Negative % (95 % CI)[a]	Positive % (95 % CI)[a]	Negative % (95 % CI)[a]
Albuminuria	38.3 (30.8,45.8)	32.5 (29.3,35.7)[b]	33.2 (26.1,40.4)	26.1 (23.2,29.1)[b]
Proliferative retinopathy	9.0 (5.3,12.7)	10.5 (8.4,12.5)	12.8 (8.2,17.3)	11.6 (9.4,13.9)

[a]Percentages are adjusted for age.
There is a significant difference between means/percentages for family history +ve and –ve with, [b]$p < 0.05$, [c]$p < 0.01$.

Table 4. Odds ratios of albuminuria by family history of hypertension (FHH)

	Men		Women	
	FHH	*p* value	FHH	*p* value
Albuminuria adjusted for:				
Age	1.34 (1.06–1.69)	0.01	1.28 (1.01–1.63)	0.04
Age, HbA_{1c}	1.30 (1.02–1.64)	0.03	1.27 (1.00–1.63)	0.06
Age, HbA_{1c}, FHDM	1.28 (1.01–1.62)	0.04	1.25 (0.97–1.60)	0.09
Age, HbA_{1c}, hypertension	1.15 (0.90–1.48)	0.26	1.18 (0.91–1.52)	0.21
Age, HbA_{1c}, systolic BP	1.18 (0.92–1.50)	0.19	1.17 (0.91–1.59)	0.23
Age, HbA_{1c}, systolic BP, anti-hypertensive therapy	1.12 (0.87–1.44)	0.39	1.13 (0.87–1.46)	0.38
Age, HbA_{1c}, hypertension, FHDM	1.14 (0.88–1.46)	0.32	1.15 (0.88–1.48)	0.31
Significance of the interaction between FHH and hypertension		0.61		0.51

AER $\geq 100\ \mu g\ min^{-1}$, there was no association between prevalence of parental history of hypertension and albuminuria in men, adjusted for age. Among women there was an association but, as with albuminuria defined as $\geq 20\ \mu g\ min^{-1}$, this was not independent of hypertension in the patient herself. Among women, but not men, parental history of diabetes was associated with albuminuria independently of age, glycaemic control, hypertension and parental history of hypertension even when albuminuria was defined as $\geq 100\ \mu g\ min^{-1}$.

There was no interaction between duration of diabetes and the effect of parental history of either hypertension or diabetes on albuminuria. There was no association between parental death from cardiovascular disease and albuminuria (OR = 1.2 for men and 1.3 for women, $p > 0.05$).

Retinopathy

There was no association between the prevalence of proliferative retinopathy and parental history of hypertension or diabetes in either sex (Table 3). There was no significant association between parental history and any grade of retinopathy either, although a slightly higher prevalence ($p > 0.05$) of retinopathy was noted in both men and women with a parental history of hypertension.

Table 5. Odds ratios of albuminuria by family history of diabetes (FHDM)

	Men		Women	
	FHDM	*p* value	FHDM	*p* value
Albuminuria adjusted for:				
Age	1.32 (1.00–1.73)	0.05	1.37 (1.03–1.82)	0.03
Age, HbA_{1c}	1.21 (0.92–1.62)	0.18	1.36 (1.01–1.82)	0.04
Age, HbA_{1c}, FHH	1.14 (0.84–1.56)	0.39	1.40 (1.02–1.92)	0.04
Age, HbA_{1c}, FHH, hypertension	1.12 (0.81–1.55)	0.49	1.41 (1.02–1.95)	0.04
Age, HbA_{1c}, FHH, systolic BP	1.11 (0.81–1.53)	0.50	1.40 (1.01–1.95)	0.04
Age, HbA_{1c}, FHH, systolic BP, anti-hypertensive therapy	1.09 (0.79–1.51)	0.61	1.47 (1.06–2.05)	0.02
Significance of the interaction between FHDM and FHH		0.58		0.48

Discussion

Nephropathy

It is widely accepted that essential hypertension has a familial component. An association between parental history of non-diabetic hypertension and diabetic nephropathy would support the hypothesis that hypertension is an antecedent of nephropathy and not just secondary to it. Such an association would also support the idea that there is familial clustering of nephropathy and that a search for genes underlying nephropathy might be warranted. Some authors have suggested that the effect of parental hypertension on blood pressure in diabetic offspring may not fully account for an association between parental hypertension and nephropathy. Thus there may be specific renal disease susceptibility genes which are in turn associated with parental hypertension.

We have demonstrated a weak association between parental history of hypertension with albuminuria in a large group of Type 1 diabetic patients. However the risk conferred by a positive family history appears to be mediated largely through hypertension in the offspring and family history does not appear to carry any additional risk of albuminuria beyond this. The observation that a parental history of hypertension is also associated with a poorer glycaemic control in men and a higher BMI in women suggests that familial predisposition to hypertension and albuminuria may not be simply genetic but may have an environmental or behavioural component. The odds ratio for albuminuria with parental hypertension of 1.3 which we observed is much lower than previously reported. Krolewski *et al*. reported an odds ratio of 3.4 for nephropathy in diabetic offspring with a parent with hypertension.[15] In Pima Indians, parental hypertension was associated with increased risk of proteinuria in offspring with non-insulin-dependent diabetes, with an odds ratio of 2.2.[36] This relationship was only observed if both parents had hypertension. In our study the number of respondents who reported that both parents had hypertension was too few to examine the association within this group separately.

Viberti *et al*. found significantly higher mean pressures in surviving parents of patients with nephropathy compared to parents of those without nephropathy.[14] In contrast, Jensen *et al*. did not find a significant association between mean parental blood pressure and macroalbuminuria in offspring, although both the prevalence of a raised blood pressure at measurement and of antihypertensive treatment were higher in parents of patients with nephropathy compared to those without.[17] Earle *et al*. found that the prevalence of parental cardiovascular disease mortality or morbidity was three times higher in parents of patients with compared to without nephropathy.[19] However, the extent to which this association was dependent on parental blood pressure was not reported and there was a non-significantly higher prevalence of hypertension in parents of patients with (21 %) compared to without (14 %) nephropathy.

Krolewski *et al*.[15] considered that predisposition to hypertension rather than hypertension *per se* was the risk factor for nephropathy, because sodium lithium countertransport (thought to be a genetic marker of hypertension predisposition)[37,38] was elevated in both those with microalbuminuria and those with macroalbuminuria, whereas hypertension prevalence was raised only in those with macroalbuminuria. However, in that study mean systolic and diastolic pressures were higher in microalbuminuric patients compared to normoalbuminuric patients. In Pima Indians, the association of parental hypertension with proteinuria in offspring was independent of mean arterial pressure and antihypertensive treatment in the offspring. Our data suggest that any association between parental hypertension and albuminuria in offspring is mediated entirely through blood pressure in the offspring. This was the case regardless of how adjustment for offspring blood pressure status was made.

Our definition of albuminuria included microalbuminuria and was based on a single urine collection. A proportion of these would not have progressed to nephropathy. We chose to examine the association of parental history with albuminuria defined as an AER $\geq 20\ \mu g\ min^{-1}$ since the usefulness of AER as a

continuous variable or dichotomized to above and below 100 μg min^{-1}, in a cross-sectional setting, is distorted by the introduction of antihypertensive therapy in those with higher AER and consequent reduction of AER. However, when the analyses were repeated with AER as a continuous variable or albuminuria defined as AER $\geq$ 100 μg min^{-1}, the conclusions were unchanged. In a previous study it was suggested that there was a stronger association between nephropathy and parental history of hypertension in patients with poor glycaemic control[15] but we did not confirm this.

We found that parental history of diabetes was also associated with albuminuria in women, independent of any confounding by blood pressure status of the patient or her parents. This association was also found with albuminuria defined as an AER $\geq$ 100 μg min^{-1} or with AER analysed as a continuous variable. Parental history of diabetes accounted for the association between parental history of hypertension and albuminuria in women. At least two-thirds of parents with diabetes had Type 2 diabetes, so our results are consistent with the reported association between insulin resistance and albuminuria,[18] and the recent report from De Cosmo *et al*. in which reduced insulin sensitivity and a higher prevalence of hyperlipidaemia and hypertension was found in parents of Type 1 diabetes patients with elevated AER.[21] In the latter study a higher prevalence of parental diabets (defined as being on treatment for diabetes) was not found. Nonetheless, the triad of insulin resistance, hyperlipidaemia, and hypertension among parents suggests that an effect of parental diabetes might be observed if parents were re-examined in a few years' time. The strength of the association between parental diabetes and albuminuria we have observed is much less than the nine-fold increase in risk of nephropathy with parental Type 2 diabetes in one study.[20] In Pima Indians, maternal diabetes was associated with a higher prevalence of proteinuria in offspring but was not statistically significant.[36] In a separate analysis of Pima Indians, the number of diabetic parents with nephropathy was associated with increased risk of Type 2 diabetes in offspring.[8] Earle *et al*. did not find an association between nephropathy and parental diabetes, perhaps because the overall prevalence of parental diabetes, based on death certification or treatment for diabetes, was low.[19] There is no obvious explanation as to why a parental history of diabetes might influence the prevalence of albuminuria in women but not in men, but the data are consistent with a stronger environmental component to albuminuria in men.

Although it might be expected that an effect of parental history would be strongest in those who develop complications after a relatively short duration of diabetes, we found no evidence of such an interaction. Our analysis of the association between parental cardiovascular disease status and albuminuria was based on parental deaths only. As such the results should be treated with caution. We did not find a statistically significant association, although the odds ratios were greater than one for both sexes.

Our study is limited in that parents were not examined. Recall of parental diabetic status was incomplete especially for hypertension status. Incomplete recall and misclassification of parental status, if random, will reduce the power of the analysis to detect associations. This is more likely to be the case for parental history of hypertension than diabetes and may partly explain why, among women, the association between albuminuria and parental diabetes was stronger than with parental hypertension. A bias in recall of parental status could bias the result towards an association. Thus it is possible that part of the association between albuminuria and family history of hypertension is due to a bias in reporting from an increased awareness of parental hypertension in hypertensive diabetes patients. Indeed among those defined as hypertensive, those who reported that they had been told by a doctor that they had hypertension in the past were slightly more likely to report a positive parental history of hypertension than hypertensive patients who were unaware of their own blood pressure status (OR = 1.3, $p < 0.05$) adjusted for age. However, the association between parental history of diabetes and albuminuria in women is unlikely to be accounted for by this recall bias as all respondents have diabetes.

Retinopathy

As hypertension is a risk factor for retinopathy and is associated with parental history, an association between parental history of hypertension and retinopathy might be expected. However, we failed to find such an association. We examined parental history in relation to proliferative retinopathy for which a familial component might be more likely but the low prevalence of proliferative retinopathy limits the power of the analysis. However, there was also no association between parental history and any grade of retinopathy.

The magnitude of any familial or genetic component to diabetic retinopathy is unclear. In the Diabetes Control and Complications Trial (DCCT) diabetic relatives of probands with retinopathy had a threefold risk of severe retinopathy. We are not aware of any other reports of familial clustering of retinopathy. The role of familial predisposition to hypertension in the clustering of retinopathy in DCCT was not reported. Only a few studies have examined the association of family history of high blood pressure with severe retinopathy.[15,39] Marshall *et al*. did not find family history of hypertension to be independently associated with retinopathy in a regression model which included the blood pressure of the proband.[39] Parental hypertension was not associated with retinopathy even without adjustment for blood pressure in the proband in a cohort from the Joslin clinic.[15] Based on our analysis and these few studies it seems that parental history of hypertension exerts no influence on retinopathy risk certainly not independently of hyperten-

sion in offspring. Neither did we find any association between parental history of diabetes and proliferative retinopathy. This is consistent with two other studies which examined this issue, although in these studies almost all the patients had Type 2 diabetes.[30,31]

There is now some support from animal studies for a genetic susceptibility to nephropathy apart from that conferred by hypertension. For hypertensive renal disease, experiments in fawn hooded rats (an animal model of hypertension which develops chronic renal failure) have demonstrated that renal complications are at least partially under separate genetic control from hypertension susceptibility.[40] Similar experiments in BB rats by the same research group suggest that diabetic renal disease susceptibility may be under separate genetic control (H. Jacobs' oral communication at International Diabetes Federation Genetics of Diabetes Satellite Meeting at Ystaad, July 1997). The implications of the data reported here are that both candidate genes for hypertension and Type 2 diabetes should be considered in the search for the genetic determinants of diabetic nephropathy in humans.

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